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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/403,897	02/22/2000	DALIT BARKAN	BARKAN=2	7830

1444 7590 10/29/2003

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	23

DATE MAILED: 10/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/403,897	BARKAN ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communicati n appears on the c ver sheet with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *2-9 and 28-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *2-9, 28-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. After review and reconsideration the finality of the Office action of Paper No. 17 is withdrawn.

2. Claim 28 has been amended. Claims 2-9 and 28-39 are under consideration.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

4. Claim 9 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 29. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). There is no difference in the scope of claim 9 and claim 29, thus the claims are substantial duplicates.

5. Claims 2-9 and 28-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) Claims 28 and 31 recite "stringent conditions". The specification states on page 13, lines 12-15 that "stringent conditions" refer to hybridization and washing conditions which those of ordinary skill in the art refer to as "stringent". However, this statement does not constitute a definition of the term stringent. The specification further provides an example stringency on page 13, lines 16-19 that is expressly noted as being "without limitation". Thus, the example of stringent conditions is non-limiting and the metes and bounds of the claims with regard to the nucleic acids which hybridizes to a nucleic acid which encodes leptin cannot be determined.

(B) Claims 2-8 recite method objectives but fail to either link said objectives to the method steps of claims upon which they depend, or provide active method steps to link the method objectives to the method of the claim upon which they depend.

6. Claims 2-9 , 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Clark et al (International Journal of Cancer, 1996, Vol. 65, pp. 186-191) in view of Tanaka et al (Journal of Biological Chemistry, June 14, 1996, Vol. 24, pp. 14610-14616), Cohen et al (Science, 1996, Vol. 274, pp. 1185-1188, reference provided by applicant as an attachment in the Appeal Brief filed May 30, 2003) and the abstract of Stevenson et al (Proc Annu Meet Am Assoc Cancer Res, 1996, Vol. 37, page A375) ~~and~~. KAC 10/19/03

Claim 28 is drawn in part to a method for treating or inhibiting tumors in mammals comprising administering to a mammal in need thereof an effective amount of leptin. Claims 2-4 embody the method of claim 28 wherein cell proliferation is inhibited for the treatment of malignancy, wherein growth factor-dependent tumors are inhibited, wherein human breast carcinoma cell proliferation is inhibited, respectively. Claim 5 embodies the method of claim 4 wherein human breast carcinoma are treated. Claim 6 embodies the method of claim 28 wherein the growth stimulatory effect of insulin on tumor cells is inhibited. Claim 7 embodies the method of claim 28 wherein the mitogenic response of tumor cells to receptor kinases, growth factors and cytokines of the group consisting of IGF-1, IL-4 and Il-9. Claim 8 embodies the method of claim 28 for inhibiting basal and insulin-induced tumor cell proliferation for the treatment of human breast cancers. Claims 9 and 29 embody the method of claim 28 wherein said active agent is leptin.

Clark et al teach that breast cancer cell lines were inhibited by contacting with the tyrosine kinase inhibitors of Herbamycin A and genistein, and that said inhibitors decrease the association of Shc with Grb2 (abstract). Clark et al teach that previous studies indicate that Herbamycin A can be administered in vivo with "tolerable toxicity". One of skill in the art would conclude that there is toxicity associated with Herbamycin A . Clark et al do not teach the administration of leptin for the inhibition of breast cancer cells, or the administration of leptin for the treatment of breast cancer.

Tanaka et al teach that a downstream effector of IRS-1 signaling is interaction with Grb2 (page 14614, second column, lines 16-19). Tanaka et al teach that Grb2 binds to a phosphotyrosine residue in the YVNI motif on IRS-1 via its SH2 domain (page 14614, second column, lines 23-25). Tanaka et al teach that cellular transformation induced by IRS-1 overexpression requires an interaction with Grb2 (page 14615, first column, last sentence of the

full paragraph), and that IGF-1 signals have been shown to promote tumorigenicity in vivo (following sentence).

The abstract of Stevenson et al teaches that Grb2 complexed with mSos or Grb2 complexed with mSos and Shc transmits the extracellular signal for the activation of the Ras GTP/GDP exchange and that a component of this complex, Shc, is constitutively phosphorylated in several breast cancer cell lines. The abstract suggests that the inhibition of the downstream signaling proteins of growth factor receptors is important (last sentence).

Cohen et al teach that leptin downregulates the insulin-dependent tyrosine phosphorylation of IRS-1 (Figure 2) and further that leptin attenuates the association of Grb2 with IRS-1 (figure 3).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute leptin for Herbamycin A in a method of treating breast cancer. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Tanaka et al on the correlation between IRS-1 signaling and tumorignesis and the signaling of IRS-1 requiring interaction with Grb2, and the suggestion of Stevenson et al on the importance of inhibiting downstream signaling from growth factor receptors in breast cancer. One of skill in the art would be motivated to substitute leptin for Herbamycin A or genistein because leptin inhibits the association between IRS-1 and Grb2 and thus has ability to inhibit the downstream signaling of IRS-1 taught to be important in tumorigeneis in vivo by Tanaka. Further, leptin is an endogenous non-toxic protein which could be administered at higher doses than Herbamycin A, and thus be more effective at inhibiting the association between Grb2 and IRS-1. .

7. Claims 2-9, 28, 29, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Clark et al (International Journal of Cancer, 1996, Vol. 65, pp. 186-191) and Tanaka et al (Journal of Biological Chemistry, June 14, 1996, Vol. 24, pp. 14610-14616) and Cohen et al (Science, 1996, Vol. 274, pp. 1185-1188) and the abstract of Stevenson et al (Proc Annu Meet Am Assoc Cancer Res, 1996, Vol. 37, page A375) as applied to claims 2-9 , 28 and 29 above, and further in view of Carter et al (U.S. Patent Application 2002193571, priority to January 7, 1997). The specific embodiments of claims 2-9 , 28 and 29 and the teachings of Clark et al and

Tanaka et al and the abstract of Stevenson et al and Cohen et al and the abstract of Stevenson et al which render obvious said claims are recited above. Claim 34 is drawn to the method of claim 28 in part wherein said active agent is a fusion protein comprising leptin. Claim 35 embodies the method of claim 34 wherein the active agent is a leptin fusion protein.

Carter et al teach a fusion protein, termed an immunoadhesin, comprising the OB protein and the Fc domain of an antibody [0237]. The OB protein is synonymous with leptin. Carter et al teach that the Fc regions of said immunoadhesins confer a longer half life on the OB protein [0264-0265].

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the leptin immunoadhesin for leptin in the method rendered obvious by the combination of Clark et al and Tanaka et al and the abstract of Stevenson et al and Cohen et al and the abstract of Stevenson et al. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Carter et al on the increased half life conferred on leptin by fusion with the Fc domain of an antibody. One of skill in the art would be motivated to increase the in vivo half life in order to sustain the dose of leptin in vivo.

8. Claims 2-8 and 28, 30-34, and 36-39 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. the instant claims are drawn to methods reliant upon the identity of genus of leptin muteins having the ability to block cell proliferation or having a sequence encoded by a nucleic acid sequence which hybridizes to the sequence which encodes leptin and wherein said hybridizing sequence has the ability to block cell proliferation , and fragments of leptin and said leptin muteins which have the ability to block cell proliferation. When given the broadest reasonable interpretation, the attribute of blocking cell proliferation is not limited to the decreased binding of IRS-1 to Grb2, which is the mechanistic basis for the ability of leptin to block cell proliferation and inhibit tumor growth (page 8, lines 5-9),. Further, there is no length limitation for the fragment, thus, any fragments of leptin and any protein variants which interacts

with other receptors or proteins to elicit inhibition of cell proliferation are within the scope of the claims. It is reasonable to conclude that the genus of proteins encompassed by the claims are highly variant because the claims are not limited with regard to the mechanism by which the variants or fragments decrease cell proliferation. The cell comprises numerous receptors and signaling pathways any of which can be subject to inhibition resulting in inhibition of growth, thus the disclosure of leptin does not adequately describe the claimed genus represented by all the potential polypeptides included within the scope of the claims. A disclosure that does not adequately describe a product itself cannot adequately describe a method of using that product. Therefore, claims 2-8, 28, 30-34 and 36-39 lack adequate written description.

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The abstract of Sastry et al (International Journal of Cancer, 1997 Jan 17, Vol. 70, No. 2, pp. 208-213); the abstract of Janes et al (Oncogene, 1994 Dec, Vol. 9, No. 12, pp. 3601-3608); the abstract of Fiddes et al (Cell Growth and Differentiation, 1995, Vol. 6, No. 12, pp. 1567-1577); and the abstract of Ito et al (Molecular and Cellular Biology, 1996, Vol. 16, No. 3, pp. 943-951).

10. All other rejections and objections as set forth in Paper No. 17 are withdrawn.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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TECH 1600

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
10/19/03